REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

1. Status Of Claims And Formal Matters

Claims 1, 3, 5, 7-10, 12, 13 and 18-18 are under consideration in this application. Claims 3 and 10 are withdrawn as allegedly directed to non-elected subject matter, claims 1, 5, 9 and 13 are amended, claims 21 and 22 are added and claim 12 is cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Applicants reserve the right to pursue the subject matter of cancelled claims in continuing application.

The recitation of a C Domain of Staphylococcus aureus Protein A inserted to the carboxy terminus of a fiber protein in claims 1 and 9 is disclosed, for example, in Example 3 of the specification as filed. Carboxy terminal has also been clarified to recite carboxy terminus in claims 1, 5, 9 and 13. Support for the adenoviral vector complexes of claims 21 and 22 are found, for example, in Examples 3-10 of the specification as filed.

No new matter has been added.

The Examiner is thanked for withdrawing rejections recited in the last Office Action not set forth in the present Office Action.

It is submitted that the claims herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§101, 102, 103 or 112. Rather, these additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2. The Claim Objections Are Overcome

Claims 3 and 10 are objected to as allegedly comprising non-elected subject matter. In response, claims 3 and 10 have been withdrawn from consideration, thereby obviating the objection.

4. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

Claims 1, 3, 5, 7, 8, 10 and 13 are rejected under 35 U.S.C. § 112, second paragraph, as

allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 1 is allegedly vague and indefinite in that it is unclear whether Applicants intend that the fusion protein of part (iii) comprises a targeting ligand selected from the group consisting of 1) CD40 ligand, 2) a scFv of anti-human CD40 and 3) an immunoglobulin Fc domain; or whether Applicants intends a fusion protein comprising an immunoglobulin Fc domain and a targeting ligand wherein the targeting ligand is either a CD40 ligand or scFv of anti-human CD40 antibody.

Claim 1 has been clarified to recite that the fusion protein comprises (a) a ligand selected from the group consisting of CD40 ligand and scFv of anti-human CD40 antibody and (b) an immunoglobulin Fc domain, thereby obviating the rejection.

Claims 3, 5, 10 and 13 are allegedly vague and indefinite as the phrase "carboxy terminal of said fiber protein" is supposedly unclear. In response, claims 3 and 10 are withdrawn from consideration and claims 5 and 13 are clarified to recite "carboxy terminus", thereby obviating the rejection.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

4. <u>The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome</u>

Claims 1, 3, 5, 7-10, 12-13 and 15-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action alleges that in view of the lack of guidance provided by the specification as well as the nature of the invention and the unpredictability of the art, the skilled artisan would have required an undue amount of experiment to make and/or use the claimed invention.

The rejection is respectfully traversed for the following reasons.

Although the Applicants do not agree with the Examiner, in the interest of expediting prosecution, claim 1 has been clarified to recite that the immunoglobulin-binding domain of Staphylococcus aureus Protein A is a C Domain of Staphylococcus aureus Protein A inserted at the carboxy terminus of the fiber protein.

It is respectfully asserted that an enabling *disclosure* is all that is required. The applicant need not describe actual embodiments or examples. Indeed, an applicant need not have reduced

the invention to practice prior to filing; the presence or absence of examples in a patent specification is only one factor in determining the extent to which claims, especially broad claims involving an unpredictable technology, are enabled.

Moreover, a prior art reference contains an enabling disclosure if a person of ordinary skill could have combined the description of the invention in the prior art reference with his own knowledge of the art to place himself in possession of the invention. It is respectfully submitted that the state of the art pertaining to the invention was not unpredictable at the time of filing the application and thus could have been relied on for guidance in practicing the claimed invention. Applicants respectfully submit that one of ordinary skill in the art can make and use the vector of the present invention by combining the teachings of the specification with what was known to one of ordinary skill in the art at the effective filing date.

As the specification points out, the present invention teaches a binary system wherein the virus and targeting ligand are each synthesized through natural biochemical pathways after which they self-associate into a stable complex (line 17, page 13). Example 2 illustrates design of the Ad5 fiber protein modified with the C domain of Staphylococcus aureus Protein A, and teaches a mechanism for attachment of targeting ligands to Ad particles. The C domain (Cd) is known to bind with high selectivity and affinity to the Fc domain of immunoglobulins (Ig). Therefore, Ad virions incorporating such Cd-modified fibers were expected to bind targeting ligands designed to contain an Fc domain. Indeed, Example 3 teaches modification of the HI-loop of Ad5 fiber and Example 4 teaches that the designed protein chimeras could be expressed at levels comparable with that of the wild type Ad5 fiber and that they possess structural and functional (Fc-binding capability) properties required for both the incorporation of these proteins into Ad virions and for binding to Fc-containing proteins.

Example 5 teaches the generation of adenoviruses containing a recombinant adenovirus containing an Ad5 fiber protein modified with the C domain of Staphlococcus aureus Protein A as well as a double reporter gene. The dual reporter gene of Example 5 is analogous to the heterologous gene of the present claims. Accordingly, the recitation of an adenovirus vector expressing a heterologous gene of the present claims is enabled by the specification as exemplified in Example 5.

Example 6 teaches design of a complementary ligand molecule, Fc-single chain antibody (scFv) fusion protein, that is capable of targeting the virus via association with its altered capsid.

Furthermore, this example teaches that both components of the newly designed gene delivery system, the viral vector and the targeting ligand, were able to associate with each other. Strong binding of the Cd-modified vectors to the ligand is demonstrated compared to virtually no binding observed with the control Ad lacking C domain in the capsid. This proves the feasibility of the formation of targeting vector complexes. As noted in this example, other targeting ligands have been constructed such as the recombinant protein comprising the extracellular domain of human CAR as reported by Dmitriev (line 5, page 51) and recombinant protein Fc-CD40L as reported by Lo (line 14, page 51).

Example 7 teaches that all Cd-modified Ad were able to employ the Fc-G28.5 ligand for CD40-mediated infection, with no significant variations between the vectors. Examples 8 and 9 teach preparation of complexes of Ad with Fc-containing targeting ligands and demonstrate their ability to transduce, or infect, CD40-positive cells. Furthermore, Example 10 demonstrates in vitro transduction of primary human dendritic cells with the CD40-targeted vectors.

In summary, the modifications made to the claims as well as the examples discussed herein together serve to obviate the rejections since they clearly convey that the present invention is indeed enabled. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph are respectfully requested.

Claims 9-10, 12-13 and 15-18 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been amended, rendering this objection moot.

The rejection is respectfully traversed for the following reasons.

Although the Applicants do not agree with the Examiner, in the interest of expediting prosecution, claims 1, 5, 9 and 13 are amended to recite a C Domain of Staphylococcus aureus Protein A inserted to the carboxy terminus of a fiber protein.

According to the Office Action, the specification described five examples of Ad vectors with fiber proteins containing the C domain of S. aureus and one example of an Ad vector with an Fc-targeting ligand fusion molecule, but the specification does not describe one example of

the claimed targeted recombinant adenovirus vector comprising both of these elements (plus a heterologous gene). Applicants respectfully disagree.

Example 11 teaches the construction of targeted adenoviral vector for selective expression of tumor-specific antigen in dendritic cells, which contains Ad fibers modified with the C-domain of S. aureus protein A, a targeting ligand and a tumor-specific antigen (i.e., a heterologous gene). Accordingly, the specification does provide examples of a claimed targeted recombinant adenovirus vector comprising fiber proteins containing the C domain of S. aureus, a ligand and a heterologous gene.

The Office Action also states that the specification does not describe how to make any adenoviral vector comprising a modified fiber protein comprising an immunoglobulin-binding domain, a gene encoding a Fc-ligand fusion protein and a heterologous gene such that the virion is capable of being assembled properly and thus propagated. Applicants respectfully disagree.

Example 11 describes the testing of expression plasmids to ensure the virion is capable of being assembled properly and thus propagated. For example, a fiber-fibritin chimera is employed asn an alternative stragety to generate the fiber-C domain chimeric gene. The fiber-fibritin protein was designed so that the structure of the domain providing for trimerization of the chimera (fibritin) is not affected by incorporation of heterologous peptides/polypeptides within the protein. In another example, expression plasmids are designed to be compatible with the fiber shuttle vectors to insert modified fiber genes into Ad genomes. Only those fiber-C domain genes whose products have successfully passed the trimerization test are utilized for future cloning. Accordingly, the specification does describe how to make an adenoviral vector such that the virion is capable of being assembled properly and propagated.

In summary, the modifications made to the claims as well as the examples discussed herein together serve to obviate the rejections since they clearly convey that the present invention is indeed enabled and that Applicant was in possession of the invention at the time of filing. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph are respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner is respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks herein, reconsideration and withdrawal of the rejections are requested. Early and favorable consideration of the application on the merits, and early Allowance of the application are earnestly solicited.

The Commissioner is hereby authorized to charge any additionally required fee for this paper, or credit any overpayment in fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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